Remarks

I. Status

Claims 28-36 are presently pending; claims 1-27 and 37-51 have been withdrawn from consideration as directed to a non-elected invention..

Applicants have amended claims 115, 127 and 132 in order to more clearly describe their invention. Support for the recitation.

II. The Rejection of Claims 28-36 Pursuant To 35 USC §112 First Paragraph

The Examiner has rejected claims 28-36 pursuant to 35 USC §112 first paragraph out of a concern that the originally filed specification fails to establish that the invention of a cross-over protein that contains at least one peptide segment whose sequence is derived from one parent protein and at least one peptide segment whose sequence is derived from a second parent protein is not described in the specification in such a way as to reasonably convey to those of ordinary skill in the art that the inventors had possession of this invention at the time of the filing of the patent application. Applicants respectfully traverse and request reconsideration.

Applicants respectfully submit that the as-filed application clearly evidences their possession of the above-mentioned aspect of the present invention. In this regard, the application states:

- "Novel proteins comprising a combination of two or more functional modules from two or more different parent proteins ... are provided." [page 5, lines 12-14]

- "The present invention provides cross-over proteins produced by chemical ligation of two or more functional protein modules derived from two or more different parent protein modules." [page 8, lines 2-4]

- "As can be appreciated, any number of modular combinations and ligation orders are possible." [page 11, lines 9-10]

- "Of particular interest are cross-over protein molecules synthesized by combining a functional module from a first protein with a functional module from a second protein. Additional functional modules can be combined from the same and/or one or more other proteins." [page 12, line 32 – page 13, line 2]

Applicants respectfully submit that the ability to combine modules from the same or different proteins is clearly enabled by the present application, which teaches how to identify functional modules (see Example 1, page 34), and how to produce cross-over proteins containing 4 such modules (see Examples 2-5). The present application clearly evidences that the inventors were in possession of this attribute of the present invention, and that it is described in terms sufficient to enable its practice by those of ordinary skill. The rejection of claims 28-36 pursuant to 35 USC §112 first paragraph may properly be withdrawn.

III. The Rejection of Claims 28-36 Pursuant To 35 USC §112 Second Paragraph

The Examiner has rejected claims 28-36 as indefinite pursuant 35 USC § 112, second paragraph. Specifically, the Examiner has professed that the use of the terms "first" and "second" to provide antecedent basis to the molecules recited in the claims renders the claims indefinite. Additionally, the Examiner has professed that the term "parent" protein renders the claims indefinite to those of ordinary skill. Applicants respectfully request reconsideration. Applicants have amended the claims in order to more clearly describe the antecedent basis for the terms "first" and "second;" and have deleted the term "parent" from the claims. Applicants submit that the rejection pursuant 35 USC § 112, second paragraph may be properly withdrawn.

The Examiner has additionally rejected the preamble of claim 28 as "being more appropriate for a library than a single protein" (citing the preamble of Applicants' claim 32).

Applicants respectfully traverse and request reconsideration. The preamble of claim 32 recites a library of *members* and then proceeds to recite a characteristic of the *members*. Accordingly, there is no inconsistency in the usage of the recite characteristics. Applicants submit that the rejection pursuant 35 USC § 112, second paragraph may be properly withdrawn.

The Examiner has additionally rejected the claims as containing "redundant" or "inherent" terminology. Applicants respectfully submit that the rejection should be withdrawn. Inclusion of recitations of "redundant" or "inherent" features permits the claims to provide proper antecedent basis for terms used in dependent claims. Applicants respectfully submit that the inclusion of recitations of "redundant" or "inherent" features thus does not render a claim indefinite. Applicants respectfully submit that the rejection is improper and should be withdrawn.

The Examiner has additionally rejected the claims in light of their recitation that the molecules have "a C-terminus and an N-terminus," in light of a concern that due to such recitation "it is unclear whether the cross-over proteins now contains at the 'left' side of the peptide sequence as the C-terminus and the 'right' side as the N-terminus." Applicants respectfully traverse and request reconsideration. Applicants submit that molecules do not have a "left" and "right" portion, and accordingly are not properly referred to using directional aids. Referring to their sequences in terms of the chemistry is believed to be both proper and preferred. Applicants respectfully submit that the rejection may be properly withdrawn.

IV. The Rejection of Claims 28-31 Pursuant to 35 USC §102(b) in light of Canne *et al.* Dawson *et al.*, Clark-Lewis *et al.*, or Gaertner *et al.*

The Examiner has rejected the claims pursuant to 35 USC §102(b) in light of Canne *et al.* (J. Am. Soc.), Dawson *et al.*, Clark-Lewis *et al.* (J. Biol. Chem.) or Gaertner *et al.*, each applied singly. Applicants respectfully traverse the rejection and request reconsideration.

Regarding the Canne *et al.* reference, the Examiner has drawn Applicants' attention to page 3002, col. 2, which recites that:

> "...the peptide segments 1 and 3 contained a carboxy-terminal-Leu-COSH ... the resulting ligations between these peptides and the amino terminal bromoacetyl groups of the segments 2 and 4 gave a –Leu[COS]Gly-sequence at the site of ligation ... condensation of 32-residue COSH segment and a 53-residue bromoacetylated gave an 86-residue product."

Applicants respectfully invite the Examiner to more carefully review the cited passage of this reference. It is submitted that segments 1 and 2 are domains of the one protein (cMyc) and that segments 3 and 4 are domains of a second protein (Max). The ligations of segment 1 to 2 or of segment 3 to 4 is thus not the ligation of peptides of different proteins, and as such is irrelevant to the claimed invention, which concerns an -[N—C] – [N—C]- linkage of peptides from different proteins.

While the Canne *et al.* reference does also teach the ligation of peptides from different proteins (i.e., the [1-2 cMyc molecule] and the [3-4 Max molecule]), the reference clearly teaches that the [1-2 cMyc molecule] and the [3-4 Max molecule] are ligated in a an ***C-terminal to C-terminal ligation*** (i.e., [N—C] – [C—N]) (see page 2999, first sentence of paragraph bridging left and right columns), and that the resulting ligation product thus possesses ***two N-termini and no C-terminus***. Accordingly, Applicants respectfully submit the Examiner's rejection of claims 28-31 in light of the Canne *et al.* reference may be properly withdrawn.

Regarding the Dawson *et al.* reference, the Examiner has drawn Applicants' attention to Figure 2 as disclosing the ligation of "two different segments." The Examiner has further drawn Applicants' attention to note 4 at page 778 of the Dawson *et al.* document. This note discloses the ligation of two pentapeptides. Applicants respectfully traverse the rejection and request reconsideration.

Applicants' invention relates not merely to the ligation of different peptide segments, but to the ligation of **functional domains** of different peptide segments **of different proteins**. The ligation discussed in Figure 2 of the Dawson *et al.* document involves two segments of the same protein (IL-8). The ligation discussed in note 4 involves two pentapeptides. No function or origin is disclosed to be associated with either peptide. Accordingly, Applicants respectfully submit the Examiner's rejection of claims 28-31 in light of the Dawson *et al.* reference may be properly withdrawn.

Regarding the Gaertner *et al.* reference, the Examiner has drawn Applicants' attention to the statement that "... a new approach for linking, through a thioether bond, the C-terminus of one unprotected polypeptide with the N-terminus of another" and has professed that such recitation establishes that "two different segments from two different polypeptides are used." Applicants respectfully traverse the rejection and request reconsideration.

Applicants respectfully submit that the Gaertner *et al.* reference is clear in stating that the "two different polypeptides" used are two polypeptide fragments of the same protein that are to be religated together (see the title: Site-Specific Religation of G-CSF Fragments through a Thioether Bond"). Applicants submit that the reference fails to teach the recitations needed to anticipate Applicants' invention of a ***method*** of producing a cross-over protein, in which:

(1) functional domains
(2) of different peptide segments
(3) of different proteins
(4) are ligated to one another.

Accordingly, Applicants respectfully submit the Examiner's rejection of claims 28-31 in light of the Gaertner *et al.* reference may be properly withdrawn.

Regarding the Clark-Lewis *et al.* reference, the Examiner has drawn Applicants' attention to the statement that "hybrids between IL-8 and the inactive IP10 protein were designed to identify structural regions and residues required for IL-8 activity." Applicants respectfully

traverse the rejection and request reconsideration. Applicants respectfully submit that the basis of the Examiner's rejection remains unclear, since the reference does not teach the ***ligation*** of *any* peptides, but rather the chemical synthesis of a an intact protein. Thus, it is irrelevant that IL-8 and IP10 are different. The present invention, as stated above, relates to the ***ligation*** of functional domains of different peptide segments of different proteins. Accordingly, Applicants respectfully submit the Examiner's rejection of claims 28-31 in light of the Clark-Lewis *et al.* reference may be properly withdrawn.

V. The Rejection of Claims 32-34 and 36 Pursuant to 35 USC §102(b) in light of Cwirla *et al.*

The Examiner has rejected claims 32-34 and 36 pursuant to 35 USC § 102(b) in light of Cwirla *et al.* Applicants respectfully traverse the rejection and request reconsideration.

Applicants respectfully submit that the pending claims are directed to methods and not compositions of matter. Prior art is thus relevant to the patentability of the pending claims only if it discloses or suggests the method being claimed. In this light, Applicants respectfully submit that the present invention relates to the ***ligation*** of functional domains of different peptide segments of different proteins. *The fusion proteins produced by Cwirla et al. are simply* ***not*** *produced through such a method. Indeed, they are formed through a completely different process: the process of in vivo protein translation.* Accordingly, Applicants submit that the rejection of claims 32-34 and 36 in light of the Cwirla *et al.* reference should be withdrawn.

VI. The Rejection of Claims 28-36 Pursuant to 35 USC §102(b) in light of Stricht *et al.*

The Examiner has rejected claims 28-36 pursuant to 35 USC § 102(b) in light of Stricht *et al.* Applicants respectfully traverse the rejection and request reconsideration.

Applicants again direct the Examiner to the language of the present method claims, which recite a process of forming cross-over proteins through the ***ligation*** of functional domains of different peptide segments of different proteins.

That method is not taught or suggested by the Stricht *et al.* document. As is evident, the Stricht *et al.* document concerns a recombinant process in which proteins are produced through ***translation***. As such, Applicants submit that the reference does not disclose the production of a "cross-over protein library" nor the formation of ***any*** protein through the act of ***ligation*** of functional domains of different peptide segments of different proteins as recited in the claims presented for examination. The rejection of claims 28-36 should be withdrawn.

VI. The Provisional Non-Statutory Double Patenting Rejections

The Examiner has provisionally rejected claims 28-31 under the judicially created doctrine of obviousness-type double patenting in light of claims 1-6 of co-pending Application Serial No. 08/945,997 or over claims of co-pending Application Serial No. 09/097,094. Applicants respectfully traverse the rejection and request reconsideration essentially for the reasons previously made of record.

As Applicants have previously stated, one looks to the claims of two applications rather than to their disclosures in order to assess the propriety of a double-patenting rejection. *Panduit Corp. v. Dennison Mfg. Co.*, 227 USPQ 337 (Fed. Cir. 1985).

As is apparent, from a comparison of claim 28 of the present application and claim 1 of the '997 application, the inventions of these applications are drawn to substantially dissimilar and clearly patentably distinct inventions. The claims of these inventions possess very different attributes:

Attribute	
Claim 28 of the Present Invention	**Claim 1 of the '997 Application**
1. Sequence of each oligopeptide must be derived from two different proteins	1. Sequence of each oligopeptide need ***not*** be derived from two different proteins
2. Each peptide must comprise a functional protein module	2. Each peptide need ***not*** comprise a functional protein module
3. No requirement that one oligopeptide possess a C-terminal thioester	3. One oligopeptide must possess a C-terminal thioester
4. No requirement that one oligopeptide possess a C-terminal thioester	4. One oligopeptide must possess an N-terminal cysteine
5. No requirement that any peptide have an unoxidized sulfhydryl side chain	5. The N-terminal cysteine must have an unoxidized sulfhydryl side chain
6. No requirement for the formation of a β-aminothioester bond between the two peptides;	6. Requires the formation of a β-aminothioester bond between the two peptides;
7. No requirement for the presence of a catalytic thiol	7. Requires the presence of a catalytic thiol
8. No requirement for the linking of the peptides via an amide bond	8. Requires the linking of the peptides via an amide bond

Applicants respectfully submit that the inventions are clearly not an "obvious variant" of one another. Applicants submit that an obviousness-type double patenting rejection is not appropriate in the present circumstance since the present application and Application Serial No. 08/945,997 do not claim the same or similar inventions and hence do not reflect an improper timewise extension of the right to exclude. The rejection should be withdrawn.

Applicants respectfully submit that an obviousness-type double patenting rejection is likewise inappropriate since the present application and Application Serial No. 09/097,094

do not claim the same or similar inventions and hence do not reflect an improper timewise extension of the right to exclude.

As is apparent, from a comparison of claim 28 of the present application and claim 1 of the '094 application, the inventions of these applications are likewise drawn to substantially dissimilar and clearly patentably distinct inventions that possess very different attributes:

Attribute	
Claim 28 of the Present Invention	**Claim 1 of the '094 Application**
1. Sequence of each oligopeptide must be derived from two different proteins	1. Sequence of each oligopeptide need ***not*** be derived from two different proteins
2. Each peptide must comprise a functional protein module	2. Each peptide need ***not*** comprise a functional protein module
3. No requirement that one oligopeptide possess a C-terminal thioester	3. One oligopeptide must possess a C-terminal thioester
4. No requirement that one oligopeptide possess a C-terminal thioester	4. One oligopeptide must possess an N-terminal cysteine
5. No requirement that any peptide be bound to a solid phase	5. At least one peptide must be bound to a solid phase before and after ligation
6. No requirement for a cleavable or uncleavable linker	6. The peptide that is bound to a solid support must be bound through a cleavable linker
7. No requirement that the N-terminus of the ligated peptide be bound to a solid phase	7. The N-terminus of the ligated peptide is bound to a solid phase
8. No requirement for the linking of the peptides via an amide bond	8. Requires the linking of the peptides via an amide bond

Applicants respectfully submit that in light of such numerous and distinct claim limitation differences, the issuance of both the '094 application and the claims of the present application

would not serve to improperly extend the "right to exclude." For example, the method to the present application could be conducted using any of oxime forming chemical ligation, thioester forming ligation, thioether forming ligation, hydrazone forming ligation, thiazolidine forming ligation, and oxazolidine forming ligation, without in any way extending the "right to exclude" provided by the '094 application, since the claims of that application concern the use of native chemical ligation. Conversely, the method of claim 1 of the '094 application could be practiced using peptide segments that did not comprise functional protein modules of pre-existing proteins without an anyway extending the "right to exclude" that would be provided by the present application upon its issuance. Applicants respectfully submit that the presently pending claims define a patentable distinct invention over the invention of the claims of the '094 application. Accordingly, it is submitted that the non-statutory obviousness-type double patenting rejections in light of the '997 and '094 applications should be withdrawn.

VII. The Provisional Obviousness Rejection Pursuant to 35 U.S.C. §102(e)/103(a).

The Examiner has provisionally rejected claims 28-31 as obvious pursuant to 35 USC §103(a) in light of co-pending Applications Serial Nos. 08/945,997 or 09/097,094. Applicants respectfully traverse the rejection and request reconsideration.

For the same reasons as discussed previously, the present claims are not obvious in light of the disclosures of Applications Serial Nos. 08/945,997 and 09/097,094. The '997 application discloses the use of native chemical ligation to ligate two peptides provided that one peptide contains an N-terminal cysteine having an unoxidized sulfhydryl side chain, and the other peptide contains a C-terminal thioester group. The '094 application describes the ability to perform native chemical ligation on peptides whose N-termini are bound to solid supports via cleavable linkers.

The present invention involves the ligation of two or more peptides. Native chemical ligation is not required by the present invention. Nor does the present invention require the binding of the N-terminus of one peptide to a solid support. Neither the '997 nor the '094

application can be said to teach or suggest such modifications. Indeed, they expressly teach these requirements. Conversely, the present invention requires that the sequences of the peptides being ligated be derived from *different* protein molecules. Neither the '997 nor the '094 application teaches or suggests such an invention.

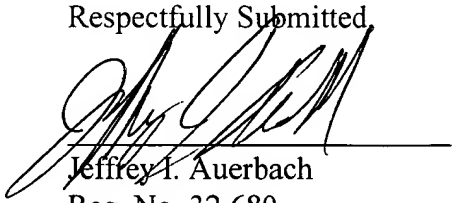
Applicants moreover *again* respectfully submit that no art cited by the Examiner teaches the **modification** of the inventions of the '997 or '094 applications that would be needed to attain the present invention. Accordingly, Applicants respectfully submit that the present claims are not obvious in light of the cited '997 and '094 applications, and that the provisional rejection of the claims on this basis may be properly withdrawn.

Applicants have respectfully submit that if no fee is required for consideration of this submission beyond those accompanying this submission. Should that determination be incorrect, then please debit account 50-0548, and notify Applicants. Having now fully responded to all of the outstanding objections and rejections made by the Examiner, Applicants respectfully submit that the present application is in condition for Allowance, and earnestly solicit early notice of such favorable action. Should the Examiner believe additional discussion would advance the prosecution of the present application, he is invited to contact the undersigned at the local telephone number listed below.

Date: 8/10/01

Liniak, Berenato, Longacre & White, LLC
6550 Rock Spring Drive, Suite 240
Bethesda, MD 20817
Telephone: (301) 896-0600
Facsimile: (301) 896-0607

Respectfully Submitted,



Jeffrey I. Auerbach
Reg. No. 32,680
Attorney for Assignee

Appendix A: The Nature of the Amendments

To facilitate the Examiner's review of the of the patentability of the present invention, Applicants have reproduced below the nature of the amendments to the claims and specification:

Amendments to the Claims:

28. **[Twice Amended]** A method of producing a cross-over protein that contains at least one peptide segment whose sequence is derived from **[**one parent**]** **a first** protein and at least one peptide segment whose sequence is derived from a second **[**parent**]** protein, said method comprising:

ligating under chemoselective chemical ligation conditions (i) at least one N-terminal peptide segment comprising a functional protein module derived from said first **[**parent**]** protein, and (ii) at least one C-terminal peptide segment comprising a functional protein module derived from said second **[**parent**]** protein having an amino acid sequence that is different from said first parent protein, wherein said N-terminal peptide segment and said C-terminal peptide segment comprise compatible reactive groups capable of chemoselective chemical ligation to one another, whereby a covalent bond is formed between said compatible reactive groups of said N-terminal peptide segment and said C-terminal peptide segment so as to produce a chemical ligation product comprising a cross-over protein having a C-terminus and an N-terminus.

30. **[Twice Amended]** The method of claim 28, wherein the first and second **[**parent**]** protein molecules from whose sequences said N-terminal peptide(s) and said C-terminal peptide(s) are derived belong to the same family of protein molecules.

31. **[Amended]** The method of claim 28, wherein said chemoselective chemical ligation is selected from the group consisting of native chemical ligation, oxime forming chemical

ligation, thioester forming ligation, thioether forming ligation, hydrazone forming ligation, [thaizolidine] **thiazolidine** forming ligation, and oxazolidine forming ligation.

32. **[Twice Amended]** A method of producing a cross-over protein library whose members contain at least one peptide segment whose sequence is derived from [one parent] **a first** protein and at least one peptide segment whose sequence is derived from a second [parent] protein, said method comprising:

ligating under chemoselective reaction conditions a plurality of unique N-terminal peptide segments each comprising one or more functional protein modules derived from said first [parent] protein and a plurality of unique C-terminal peptide segments each comprising one or more functional protein modules derived from a second [parent] protein having an amino acid sequence that is different from said first [parent] protein, wherein said N-terminal peptide segments and said C-terminal peptide segments comprise compatible reactive groups capable of chemoselective chemical ligation to one another, whereby a covalent bond is formed between said compatible reactive groups of said N-terminal peptide segments and said C-terminal peptide segments so as to produce a plurality of chemical ligation products comprising a plurality of unique cross-over proteins each having a C-terminus and an N-terminus.

33. **[Amended]** The method of claim 32, wherein said plurality of N-terminal peptide segments are obtained by cross-over ligation of two or more different [parent] **families of** protein molecules.

34. **[Amended]** The method of claim 32, wherein said plurality of C-terminal peptide segments are obtained by cross-over ligation of two or more different [parent] **families of** protein molecules.

35. **[Twice Amended]** The method of claim 32, wherein the first and second **[**parent**]** protein molecules from whose sequences said N-terminal peptide(s) and said C-terminal peptide(s) are derived belong to the same family of protein molecules.

Amendments to the Specification:

The paragraph beginning at page 19, line 25 and continuing to page 20, line 9 has been amended as follows:

-- Assays of particular interest employ receptors provided by tissues or cell preparations, synthetic preparations and the like. Receptors of particular interest are lipid membrane-bound receptors generated by lipid matrix-assisted chemoselective chemical ligation as described in **[**co-pending application U.S. Serial No. [to be assigned] filed August 31, 1998 (Attorney Docket No. GRFN-O28/00US)**]** **U.S. Patent Application Serial No. 144,964**. Screening for binding of a cross-over protein ligand comprising one or more chromophores to a target receptor is preferably performed in a FRET assay. Ligand binding can be measured by any number of methods known in the art for FRET analyses, including steady state and time-resolved fluorescence by monitoring the change in fluorescence intensity, emission energy and/or anisotropy, for example, through energy transfer from a donor moiety to an acceptor moiety of the FRET system. (See, e.g., Wu et al., Analytical Biochem. (1994) 218: 1-13). FRET assays allow not only distance measurements, but also resolution of the range of donor- to-acceptor distances. FRET also can be used to show that the ligand and/or target receptor exists alternately in a single conformational state, or with a range of donor-to-acceptor distances when in a different state, such as when bound to a ligand. More than one donor-acceptor pairing may also be included.

Appendix B: The Pending Claims

Claims 28-36 are pending. To facilitate the Examiner's review of the of the patentability of the present invention, Applicants have reproduced below the presently pending claims:

28. **[Twice Amended]** A method of producing a cross-over protein that contains at least one peptide segment whose sequence is derived from a first protein and at least one peptide segment whose sequence is derived from a second protein, said method comprising:

ligating under chemoselective chemical ligation conditions (i) at least one N-terminal peptide segment comprising a functional protein module derived from said first protein, and (ii) at least one C-terminal peptide segment comprising a functional protein module derived from said second protein having an amino acid sequence that is different from said first parent protein, wherein said N-terminal peptide segment and said C-terminal peptide segment comprise compatible reactive groups capable of chemoselective chemical ligation to one another, whereby a covalent bond is formed between said compatible reactive groups of said N-terminal peptide segment and said C-terminal peptide segment so as to produce a chemical ligation product comprising a cross-over protein having a C-terminus and an N-terminus.

29. The method of claim 28 further comprising the step of repeating said ligating one or more times with one or more second peptide segments selected from the group consisting of an N-terminal peptide segment and a C-terminal peptide segment.

30. **[Twice Amended]** The method of claim 28, wherein the first and second protein molecules from whose sequences said N-terminal peptide(s) and said C-terminal peptide(s) are derived belong to the same family of protein molecules.

31. **[Amended]** The method of claim 28, wherein said chemoselective chemical ligation is selected from the group consisting of native chemical ligation, oxime forming chemical

ligation, thioester forming ligation, thioether forming ligation, hydrazone forming ligation, thiazolidine forming ligation, and oxazolidine forming ligation.

32. **[Twice Amended]** A method of producing a cross-over protein library whose members contain at least one peptide segment whose sequence is derived from a first protein and at least one peptide segment whose sequence is derived from a second protein, said method comprising:

ligating under chemoselective reaction conditions a plurality of unique N-terminal peptide segments each comprising one or more functional protein modules derived from said first protein and a plurality of unique C-terminal peptide segments each comprising one or more functional protein modules derived from a second protein having an amino acid sequence that is different from said first protein, wherein said N-terminal peptide segments and said C-terminal peptide segments comprise compatible reactive groups capable of chemoselective chemical ligation to one another, whereby a covalent bond is formed between said compatible reactive groups of said N-terminal peptide segments and said C-terminal peptide segments so as to produce a plurality of chemical ligation products comprising a plurality of unique cross-over proteins each having a C-terminus and an N-terminus.

33. **[Amended]** The method of claim 32, wherein said plurality of N-terminal peptide segments are obtained by cross-over ligation of two or more different families of protein molecules.

34. **[Amended]** The method of claim 32, wherein said plurality of C-terminal peptide segments are obtained by cross-over ligation of two or more different families of protein molecules.

35. **[Twice Amended]** The method of claim 32, wherein the first and second protein molecules from whose sequences said N-terminal peptide(s) and said C-terminal peptide(s) are derived belong to the same family of protein molecules.

36. The method of claim 32, wherein said chemoselective chemical ligation is selected from the group consisting of native chemical ligation, oxime forming chemical ligation, thioester forming ligation, thioether forming ligation, hydrazone forming ligation, thiazolidine forming ligation, and oxazolidine forming ligation.